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circumference. Neurological findings were non-specific in all of these cases. In Case 1 an air encephalogram was necessary to localize the abnormality. Two other air studies on psychotic children showed diffuse ventricular enlargement.

CONCLUSION

Sixty-two psychotic children were found among 1216 children referred to a diagnostic and treatment centre for the mentally retarded.

The family histories of the psychotic children were significantly different from those of a control group admitted to a children's hospital for tonsillectomy. Twenty-six psychotic children had at least one inadequate parent. History, physical examination and laboratory evidence favoured an organic brain disorder in at least 46 of these psychotic children, but none showed cerebral palsy or gross motor handicap on physical examination. Possible explanations for this observation are discussed.

It is concluded that an inadequate family background is often associated with the development of psychosis, but a severe disturbance of temporal and frontal lobe function may produce psychotic symptoms in the child with or without familial predisposition.

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REFERENCES

1. ZARFAS, D. E.: *Canad. Med. Ass. J.*, **88**: 192, 1963.
2. GIBBS, E. L. AND GIBBS, F. A.: *Science*, **138**: 1106, 1962.
3. GREULICH, W. W. AND PYLE, S. I.: Radiographic atlas of skeletal development of the hand and wrist, 2nd ed., Stanford University Press, Stanford, Calif., 1959.
4. FISH, B.: *J. Nerv. Ment. Dis.*, **125**: 1, 1957.
5. CROTHERS, B. AND PAINE, R. S.: The natural history of cerebral palsy, Harvard University Press, Cambridge, Mass., 1959, p. 231.
6. HENDERSON, J. L.: Cerebral palsy in childhood and adolescence, E. & S. Livingstone, Ltd., Edinburgh, 1961.
7. CREAK, E. M.: *Brit. J. Psychiat.*, **109**: 84, 1963.
8. BENDER, L.: *Amer. J. Orthopsychiat.*, **17**: 40, 1947.
9. SLATER, E., BEARD, A. W. AND GLITHERO, E.: *Brit. J. Psychiat.*, **109**: 95, 1963.
10. COLBERT, E. G., KOEGLER, R. R. AND MARKHAM, C. H.: *A.M.A. Arch. Gen. Psychiat.*, **1**: 600, 1959.

Mental Retardation: Methods of Diagnosis and Some Recently Described Syndromes

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ABSTRACT

Reduction of intelligence should be differentiated from interference with the use of intelligence by such non-intellective factors as partial deafness and emotional disturbance. The parents of a retarded child want an assessment, a prediction of the eventual achievement level, and a causal explanation if possible. There are varying degrees of knowledge of causation, from recognition of reduced intelligence only, to an understanding of the mechanism of causation in considerable detail from primary cause to ultimate consequence, as in phenylketonuria or isoimmunization. A diagnosis should be as complete as possible, using available modern techniques of investigation, such as chromatography and cytogenetic studies.

Among the recently described syndromes associated with mental retardation are: (1) spastic paralysis and congenital ichthyosis; (2) Rud's syndrome; (3) deaf-mutism, infantilism, ataxia and a disturbance of hormone metabolism; and (5) sex-linked deaf-mutism.

A DOCTOR confronted with a patient who may be mentally retarded is faced, in general, with three diagnostic problems. First, is there reduction of intelligence or are non-intellective factors interfering with the use of such intelligence as the child has? There may be special disabilities, such as deafness, especially partial deafness, or poor vision, which sometimes impair school performance, emotional disturbances or unfavourable home circumstances. In some instances the decision is difficult or impossible, especially in a very young child, and it may be wise to inform the parents that the child is functioning subnormally and must be assessed again in three or six months when a prediction of the child's future may be possible. This information is what the parents want. They want to know what the matter is and if any treatment can be given, but they want to know, in particular, whether the child will be educable or not, and in what sort of school. The second diagnostic problem concerns the degree of retardation, and upon this diagnosis the prediction of the child's future depends: whether the child will ever be trainable, educable or employable. The third diagnostic problem is, granted that a child is mentally retarded, what is the diagnosis? The diagnosis of mental retardation is a symptomatic diagnosis only.

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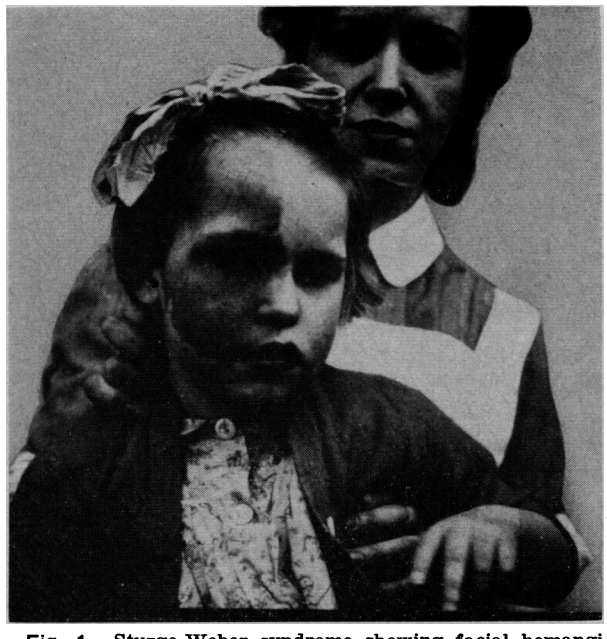

Fig. 1.—Sturge-Weber syndrome showing facial hemangioma and contralateral hemiplegia.

Diagnoses may be classified in increasing degrees of completeness, as follows:

1. Mental retardation. This is a symptomatic diagnosis, and may be qualified as to the degree of subnormality.

2. Mental retardation with associated physical symptoms, such as hydrocephalus or spastic paralysis. This narrows down the diagnosis in so far as some causes may be excluded, but each of these groups is heterogeneous. There are many causes of hydrocephalus and of spastic paralysis. Different patients with the same symptoms may have different diseases.

3. Mental retardation of a specific type, such as the Sturge-Weber syndrome. This condition can be diagnosed clinically. We cannot say, as we can of spastic paralysis, that it may be brought about in half a dozen different ways. It is a curious condition, characterized by facial hemangioma over the distribution of the trigeminal nerve and a similar hemangioma of the meninges of the same side, with underlying cortical atrophy and cerebral cortical calcification. There is contralateral hemiplegia, and epilepsy is usual (Fig. 1). It seems improbable that this syndrome would have more than one cause; when this condition is diagnosed we assume homogeneity, and the next patient with Sturge-Weber syndrome will have it for the same reasons. From 1866 until 1959, the diagnosis of mongolism has been of this class. We have assumed with confidence that the group is homogeneous.

4. Mental retardation of a specific type with known etiology. This now includes mongolism and true microcephaly, for instance. We know that mongolism is due to a chromosome anomaly. We know that true microcephaly is due to a rather rare recessive gene (Fig. 2).

5. Mental retardation of specific type and known etiology and with some knowledge of how the cause leads to the effect. Such knowledge we may have in various degrees of detail. Examples are gargoylism, isoimmunization and phenylketonuria. We are able to recognize gargoylism clinically (Fig. 3). The pattern of inheritance indicates that the condition is due to a recessive gene. We know that there is a disturbance

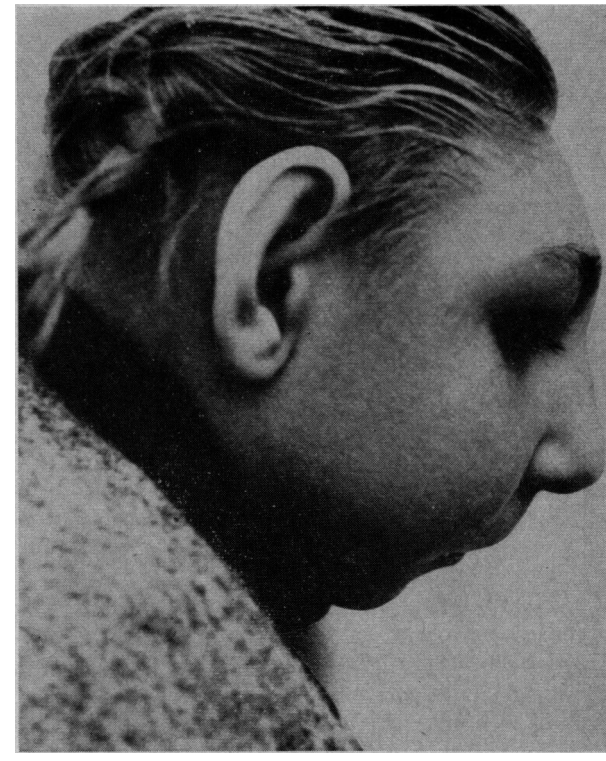

Fig. 2.—True microcephaly, with characteristic profile. Receding forehead and receding chin.

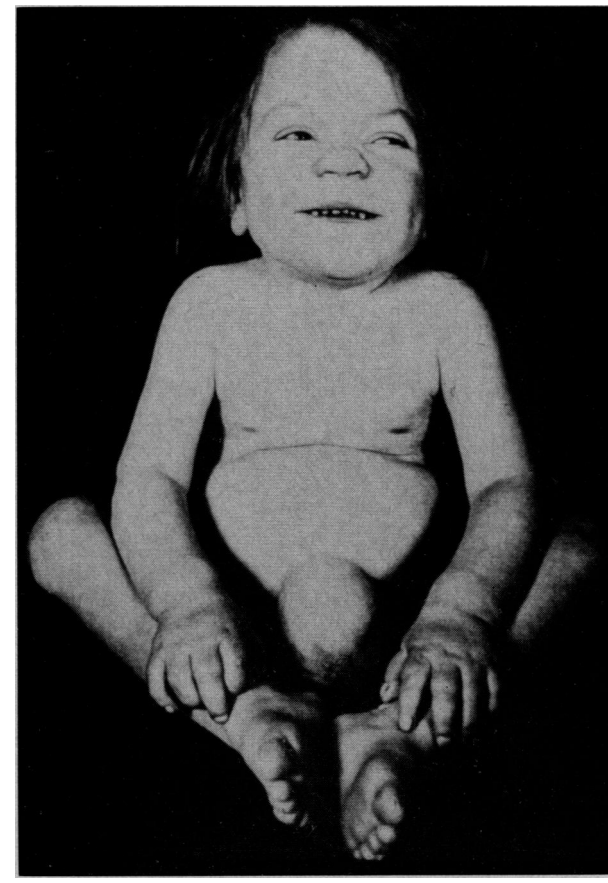

Fig. 3.—Gargoylism (Hurler's disease). Large head and characteristic facial appearance, short neck, protuberant abdomen (due to enlarged liver) and umbilical hernia.

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of lipid metabolism and that sphingolipid is deposited in neurons and in various body organs and tissues. We know that isoimmunization is usually due to maternal antibodies of a Rhesus-negative mother entering the circulation of her Rhesus-positive fetus, causing hemolysis, leading to a rising bilirubin level in her child's blood, and damage to brain tissue by bilirubin deposition and perhaps by anoxia. The disease can be diagnosed before birth by blood tests and the child can be treated at birth. We know that phenylketonuria is due to a rare recessive gene, and that an enzyme is lacking that should convert phenylalanine to tyrosine, that phenylalanine and its metabolites accumulate with toxic results, and that there is some deprivation of melanin with consequent dilution of hair, eye and skin colour.

Thus there are many degrees of diagnosis. It is our aim to diagnose with as much detail and precision as possible; to do so we need all the help we can get. A number of special investigations have been mentioned above in discussing the matter of diagnosis. Chromosome anomalies should be suspected in any condition characterized by multiple congenital malformations. A number of different chromosome anomalies associated with mental retardation are now known (Table I). Buccal smears

TABLE I.—HUMAN CHROMOSOME ABNORMALITIES ASSOCIATED WITH MENTAL RETARDATION

Klinefelter's syndrome, XXY	Jacobs and Strong[32]	1959
Turner's syndrome, XO	Ford *et al.*[33]	1959
Triplo-X syndrome, XXX	Jacobs *et al.*[34]	1959
Mongolism, trisomy 21	Lejeune *et al.*[31]	1959
Mongolism, 13:15/21 transolocation	Polani *et al.*[37]	1960
Mongolism, 21:22/21 translocation	Fracarro, Kaijser and Lindsten[38]	1960
Trisomy 17-18	Edwards *et al.*[35]	1960
Trisomy 13-15	Patau *et al.*[36]	1960
Isochromosome, long arm X	Fraccarro, Kaijser and Lindsten[38]	1960
Duplication, long arm 13	Delhanty and Shapiro[39]	1962
Ring chromosome, 16-18	Wang *et al.*[40]	1962

are simple to obtain and enable a diagnosis of Klinefelter's or Turner's syndrome to be made. Inborn errors of metabolism have sometimes been discovered by chromatographic screening of a large population of mentally retarded subjects (Table II). It is worth considering this form of investigation whenever the family history suggests hereditary causation. Inborn errors of metabolism are usually caused by rare recessive genes, which may result in a familial tendency and an increased likelihood of parental consanguinity. Some biochemical tests are simple to do in practice, e.g. the Phenistix test for phenylketonuria. There is also a spot test for the presence of mucopolysaccharides in urine, by which gargoylism may be detected in doubtful cases.

X-ray studies are of diagnostic value in several diseases, such as the Sturge-Weber syndrome. Cerebral calcification occurs sometimes in tuberous sclerosis and toxoplasmosis. In tuberous sclerosis there may also be cysts in the bones of the hands.

TABLE II.—INBORN ERRORS OF METABOLISM ASSOCIATED WITH MENTAL RETARDATION*

Phenylketonuria	Fölling[41]	1934
Galactosemia	Townsend, Mason and Strong[46]	1951
Cretinism and goitre	Stanbury and Hedge[42]	1950
Cretinism with failure of coupling of iodotyrosines	Stanbury, Ohela and Pitt-Rivers[44]	1955
Cretinism and deaf-mutism	McGirr, Hutchison and Clement[45]	1959
Cystathioninuria	Harris, Penrose and Thomas[50]	1959
Argininosuccinicaciduria	Allan *et al.*[43]	1958
Maple syrup disease	Westall, Dancis and Miller[47]	1957
Citrullinuria	McMurray *et al*[49]	1962
Hyperammonemia	Russell *et al.*[48]	1962

*Some dates listed here refer to the year when the biochemical anomaly was elucidated, not when the clinical syndrome was described.

In the craniostenoses, fusion of suture lines and abnormal-shaped skulls can be detected in doubtful cases of such conditions as oxycephaly and scaphocephaly. Air studies, such as air encephalography and ventriculography, may assist in the diagnosis of cortical atrophy and in detecting the site of obstruction in hydrocephalus. This is of practical importance, since operative treatment may relieve obstruction in infancy.

An electroencephalogram may provide evidence of an epileptic tendency or of a focal lesion, such as temporal lobe epilepsy.

An examination of white blood cells may also provide information of value—for instance, the presence of vacuoles or granules in the lipidoses. There are, as well, other biochemical investigations by which various diseases can be diagnosed. Cretinism is now more likely to be due to an inborn error of metabolism than to nutritional deprivation. Protein-bound iodine values may suggest cretinism, but radioiodine studies are necessary to diagnose the inborn errors of metabolism. There are three different metabolic blocks known in the pathology of iodine metabolism.

I have not covered all possible investigations that may help in the diagnosis of mental retardation, but there are many, and although it is not convenient to carry out extensive investigations on every case in practice, it is imperative to make use of those that may be indicated by clinical findings. The field of mental retardation is a branch of medicine in which clinical research is still necessary. New syndromes continue to be reported, and any general practitioner may encounter in a mentally retarded patient some collection of symptoms never previously described. Progress in knowledge in this subject largely consists in the discovery and collection of more and more uncommon diseases associated with mental retardation.

I should like now to outline a few recently described syndromes in which I have been interested. The first is characterized by mental retardation, spastic paralysis and congenital ichthyosis. This was first described in detail by Sjögren and Larsson[1] in 1957. These workers carried out a survey

in a part of Sweden and found 28 cases of this nature in 16 families. The three symptoms segregated clearly, that is to say, all affected subjects had all three symptoms; unaffected sibs had none of them. Three also had retinal lesions. The authors established that the condition was due to an autosomal recessive gene.

At the time of this publication, I was investigating two sibs with this syndrome, and reported details of the family in the same year.[2] It happened that the parents were Greek Cypriots who had migrated to Great Britain. Later, a mentally retarded girl with the same syndrome was admitted. She was English, and the daughter of consanguineous parents.[3] The causative gene therefore appears to be widespread, and since 1957 a number of cases have been reported in the U.S.A.,[4-6] Great Britain,[7, 8] Germany,[9] Italy,[10] Israel,[11] France,[12] and Canada.[13]

Ichthyosis is a thickening, roughness and scaliness of the skin. In mild form, it is called xeroderma, which is common without associated symptoms in people of normal intelligence and shows dominant inheritance. As a part of this syndrome, however, it is more severe, and the skin shows brown pigmentation in the affected areas (Fig. 4). The neck, axillae and abdomen are the most pigmented areas in the cases I have seen. This is a syndrome easily recognized, but there is a quite different syndrome of which xeroderma is a part. This condition is of particular interest because it demonstrates how, starting with clinical observations, a syndrome becomes more and more clearly defined in the course of time as more reports are published and more investigations are carried out. Even yet, the syndrome is not quite clearly defined. It is illuminating to examine the historical development of our knowledge of this condition.

In 1927 Rud[14] reported an adult male with ichthyosis, infantilism, dwarfism, epilepsy, hyperchromic, macrocytic anemia, tetany and polyneuritis. No mental test was done, but the author recorded that "His [the patient's] reading interests and pleasure over trifles are somewhat puerile." He described an adult female in 1929 with ichthyosis, infantilism, partial gigantism and diabetes mellitus.[15] In 1935 van Bogaert[16] reported two young adult males with mental deficiency, ichthyosis, infantilism and epilepsy. In 1939 Stewart[17] described a case of ichthyosis, idiocy, infantilism and epilepsy. This patient also had arachnodactyly and blindness due to lens opacities and pigmentation of the retina.

Thus, there was a total of five case records up to 1939 of subjects with a variety of symptoms. It is difficult to be sure up to this time if all subjects reported have the same condition. However, it seems likely that they may suffer from a syndrome central to which is the combination of ichthyosis, infantilism, a tendency to epilepsy and some reduction of intelligence, and a variety of other symptoms that may or may not be present. Infantilism means some failure in sexual maturation. The ichthyosis in these patients was not severe and pigmented, as in the Sjögren-Larsson syndrome, but consisted of a mild generalized scaliness such as is often designated xeroderma.

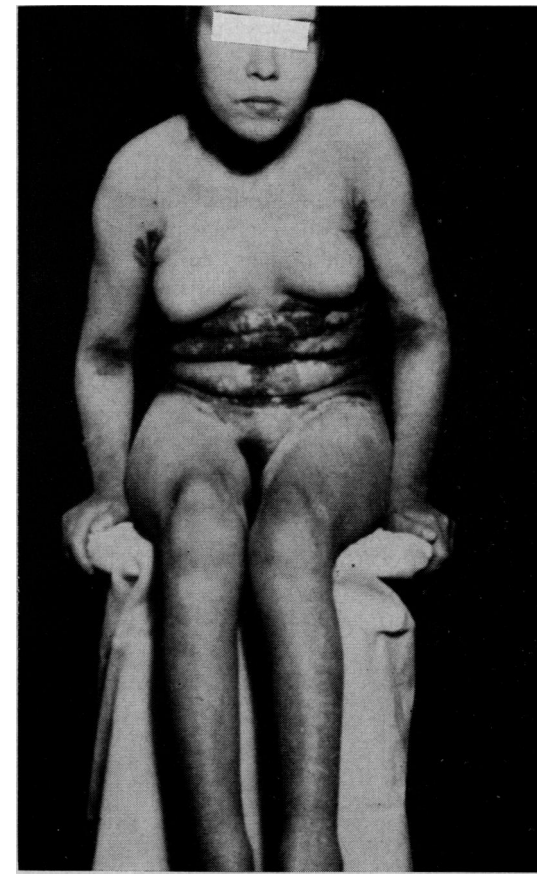

Fig. 4.—Mental retardation, spastic paralysis and ichthyosis. Some ichthyotic areas show brown pigmentation.

In 1954 McGillivray[18] described an adult female with mental deficiency, xeroderma, infantilism and epilepsy. In 1956 Ewing[19] reported three females and one male with ichthyosis, mental deficiency and epilepsy, and another female with xeroderma, epilepsy and mental deficiency, presumably having the same skin condition in milder degree. One of the females had talipes equinovarus and the male had poorly developed secondary sex characters. In addition, one of the affected females, whose sexual development appeared to be normal, had a mentally subnormal brother of small stature, with poorly developed genitalia and xeroderma. This accounts for a total of 11 such cases up to 1956. Ewing's cases, found in a survey of mentally retarded patients, show for the first time an instance of a familial tendency. This example of familial tendency also shows the variability in sexual maturation, since the male with poorly developed genitalia had an affected sister who appeared to be normally sexually developed. However, biochemical investigations would be required to establish whether her production of sex hormones was normal.

In 1960 Lynch *et al.*[20] reported a young male with congenital ichthyosis and hypogonadism. There was paucity of pubic and axillary hair. The penis and testes were small and the voice was high-pitched. Testicular biopsy showed generalized atrophy, lack of spermatogenesis, almost total absence of Leydig cells and hyalinization of the connective tissue in some areas. Hormonal assay for pituitary gonadotrophins showed a very low titre. Buccal smears were normal.

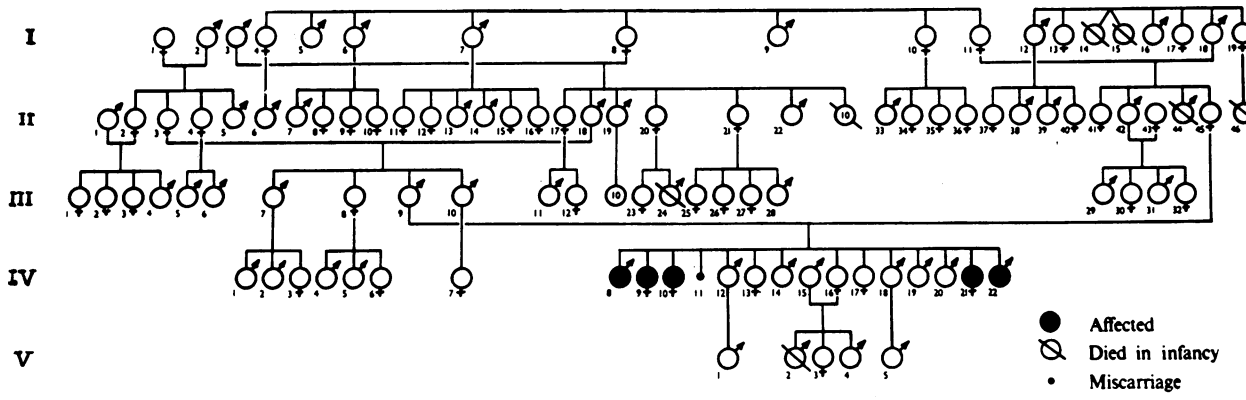

Fig. 5.—Pedigree of family with mental retardation, ataxia, deaf-mutism and a disorder of hormone metabolism. The parents of the affected sibs are second cousins (Richards and Rundle[24]).

Two male first cousins, once removed, on the mother's side had ichthyosis and hypogonadism, testicular inactivity being confirmed by biopsy. In these two, pituitary gonadotrophins were reduced. Chromosome complements were normal. Two deceased male relatives on the maternal side had the same condition according to the description of relatives. Fourteen members of the family had various congenital defects, particularly pectus excavatum, and one female first cousin had ichthyosis. Lynch did not comment on the intelligence level in these cases and no tests were carried out. Electroencephalographic (EEG) studies were not reported. The family reported by Lynch showed a familial tendency, with a pattern of inheritance suggesting sex linkage or sex influence. Ichthyosis and infantilism are common to the patients investigated, and the detection of low pituitary gonadotrophin excretion is an important addition to our knowledge of this syndrome.

In the same year (1960) Benincasa-Stagui, Giordano and Lintas[21] reported five patients with ichthyosis and mental deficiency, two having developed genitalia and one, late onset of menarche. Three had immature EEG patterns. Wright,[22] in 1961, reported a Negro boy aged 8 with congenital ichthyosis, mental retardation, dwarfism and alopecia. His intelligence quotient (I.Q.) was 31. His bone age was 5 years. There was a family history of epilepsy.

This accounts for a probable total of 24 cases of this nature. Two more were described by my colleagues, Dr. Yorke-Moore and Mr. Rundle,[23] in 1962. The propositus was a mentally retarded male with ichthyosis and infantilism. At the age of 26, his testes were undescended, pubic and axillary hair was scanty, and he did not have to be shaved. His I.Q. was 34. Not all epiphyses were united in the hands, so that there was retarded bone maturation. He has had no fits, but the EEG was reported to be abnormal and consistent with an epileptic diathesis. Buccal smears and chromosome complement were normal. He had bilateral pes cavus and bilateral nerve deafness, which was not complete. Extensive biochemical investigations revealed much reduced urinary gonadotrophin, reduced testicular hormone and increased dihydroepiandrosterone (D.H.A.).

His adult brother has been married for a few years but has no children. He never has to shave. He has xeroderma and is probably of dull mentality. He also has reduced urinary gonadotrophin output. There are two normal brothers and four normal sisters.

Summarizing the evidence now available, we find a syndrome characterized by ichthyosis, infantilism, a tendency to reduction of intelligence and an epileptic tendency. The few cases investigated have had reduced pituitary gonadotrophin output in the urine. There is a familial tendency, and it is probable that the disease is of genetic origin. There is some evidence of sex influence, as males may be more often and more severely affected. If it is a genetic disorder, the gene shows variability of expression and a number of other symptoms may be present.

I shall mention very briefly two other syndromes of interest.

One family has been reported[24] in which five of 13 sibs were mentally retarded deaf-mutes with infantilism, ataxia and a disturbance of hormone metabolism. The three adult females had no breast tissue and never menstruated. The adult male showed no active spermatozoa. There was also some peripheral muscular wasting. The parents are second cousins (Fig. 5). Steroid investigations produced rather complicated results, but pregnandiol,

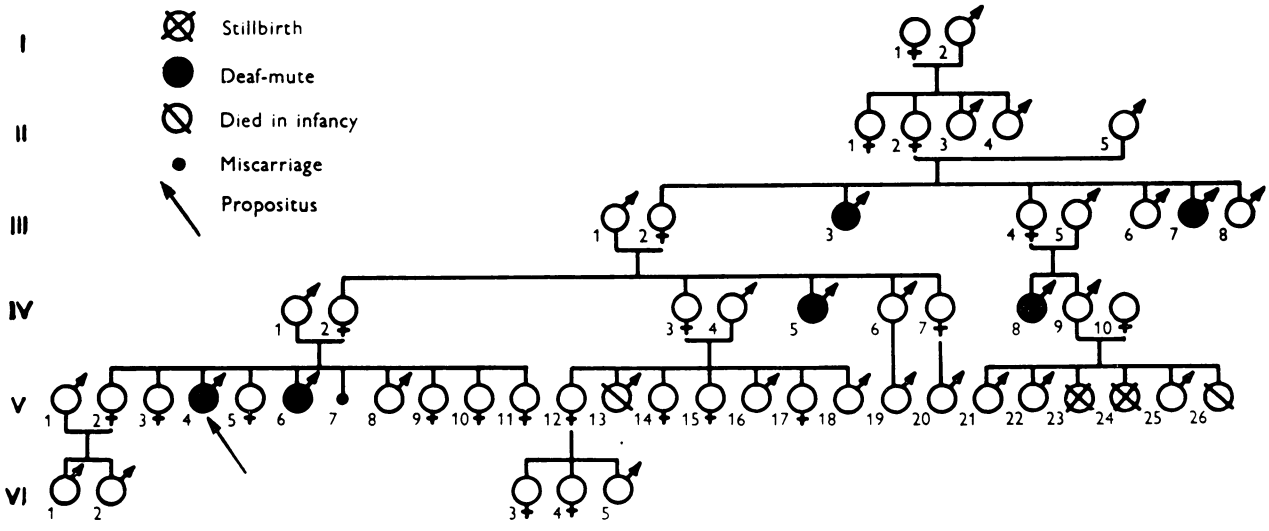

Fig. 6.—Pedigree of family with six cases of deaf-mutism. (Thanks are due to Professor L. S. Penrose for permission to republish Fig. 6, originally published in the *Annals of Human Genetics*.[30])

derived from progesterone, was almost absent from the urine and there was evidence suggesting that this condition might be due to an inborn error of metabolism, with a metabolic block in steroid metabolism. The only other report which is almost certainly of the same condition was published in a German medical journal in 1919.

Finally, a few examples have been described of recessive sex-linked deaf-mutism. There were reports from the U.S.A.,[25, 26] Japan,[27] Australia,[28] and Belgium.[29] I reported one family with this condition recently.[30] There were six affected males in all, in four different sibships (Fig. 6). This is characteristic of sex linkage, males being affected, but normal female carriers transmitting the disorder. No biochemical abnormalities were found. Mental retardation was mild and not always present in these cases.

The syndromes described above are characterized by the presence of observable abnormalities which might be encountered from time to time in general medical practice. They are rare, but mentally retarded subjects are afflicted by a large number of diseases, most of them rare, and there are many more not yet diagnosed. This is therefore a branch of study in which the general practitioner can play an important part, not only in the detection of mental retardation as such, but also in clinical research by noting and recording any new or unusual combination of symptoms.

Figs. 1, 2 and 3 belong to the Fountain Hospital collection, for the loan of which I am grateful to Dr. B. H. Kirman.

REFERENCES

1. SJÖGREN, T. AND LARSSON, T.: *Acta Psychiat. Scand.*, 132 (Suppl. 113): 1, 1957.
2. RICHARDS, B. W., RUNDLE, A. T. AND WILDING, A. ST.J.: *J. Ment. Defic. Res.*, **1**: 118, 1957.
3. RICHARDS, B. W.: *Brit. Med. J.*, **2**: 714, 1960.
4. LINK, J. K. AND ROLDAN, E. C.: *J. Pediat.*, **52**: 712, 1958.
5. BAAR, H. S., FRIGYESI, T. AND MAUTNER, H. J.: *J. Maine Med. Ass.*, **51**: 189, 1960.
6. WILLIAMS, R. D. B. AND TANG, I. L.: *Amer. J. Dis. Child.*, **100**: 924, 1960.
7. COLVER, T. AND GRAHAM, J. T.: *Brit. Med. J.*, **2**: 1522, 1960.
8. TIMPANY, M. M.: *Lancet*, **1**: 1132, 1962.
9. GREITHER, A.: *Hautarzt*, **10**: 403, 1959.
10. BENINCASA-STAGUI, E., GIORDANO, A. AND LINTAS, A.: *Lav. Neuropsichiat.*, **27**: 9, 1960.
11. WALLIS, K. AND KALUSHINER, A.: *Ann. Paediat. (Basel)*, **194**: 115, 1960.
12. SCHACTER, M.: *Acta Pediatrica Espanola*, **20**: 219, 1961.
13. ZALESKI, W. A.: *Canad. Med. Ass. J.*, **86**: 951, 1962.
14. RUD, E.: *Hospitalstidende*, **70**: 525, 1927.
15. *Idem*: *Ibid.*, **72**: 426, 1929.
16. BOGAERT, L. VAN: *Rev. Neurol. (Paris)*, **63**: 353, 1935.
17. STEWART, R. M.: *J. Ment. Sci.*, **85**: 256, 1939.
18. MCGILLIVRAY, R. C.: *Amer. J. Ment. Defic.*, **59**: 67, 1954.
19. EWING, J. A.: *Ibid.*, **60**: 575, 1956.
20. LYNCH, H. T. *et al.*: *Amer. J. Hum. Genet.*, **12**: 440, 1960.
21. BENINCASA-STAGUI, E., GIORDANO, A. AND LINTAS, A.: *Lav. Neuropsychiat.*, **27**: 13, 1960.
22. WRIGHT, C. E.: *Bull. Sch. Med. Univ. Maryland*, **46**: 22, 1961.
23. YORKE-MOORE, M. E. AND RUNDLE, A. T.: *J. Ment. Defic. Res.*, **6**: 108, 1962.
24. RICHARDS, B. W. AND RUNDLE, A. T.: *Ibid.*, **3**: 33, 1959.
25. DOW, G. S. AND POYNTER, C. I.: Quoted by Mitsuda, H., Inouc, S. and Kazama, Y.: *Japanese Journal of Genetics*, **27**: 142, 1952.
26. SATALOFF, J., PASTORE, P. N. AND BLOOM, E.: *Amer. J. Hum. Genet.*, **7**: 201, 1955.
27. MITSODA, H., INOUC, S. AND KAZAMA, Y.: *Japanese Journal of Genetics*, **27**: 142, 1952.
28. PARKER, N.: *Amer. J. Hum. Genet.*, **10**: 196, 1958.
29. DERAEMAEKER, R.: *Acta Genet. (Basel)*, **8**: 228, 1958.
30. RICHARDS, B. W.: *Ann. Hum. Genet.*, **26**: 195, 1963.
31. LEJEUNE, J., GAUTIER, M. AND TURPIN, R.: *C. R. Acad. Sci. (Paris)*, **248**: 602, 1959.
32. JACOBS, P. A. AND STRONG, J. A.: *Nature (London)*, **183**: 302, 1959.
33. FORD, C. E. *et al.*: *Lancet*, **1**: 711, 1959.
34. JACOBS, P. A. *et al.*: *Ibid.*, **2**: 423, 1959.
35. EDWARDS, J. H. *et al.*: *Ibid.*, **1**: 787, 1960.
36. PATAU, K. *et al.*: *Ibid.*, **1**: 790, 1960.
37. POLANI, P. E. *et al.*: *Ibid.*, **1**: 721, 1960.
38. FRACCARO, M., KAIJSER, K. AND LINDSTEN, J.: *Ibid.*, **1**: 724, 1960.
39. DELHANTY, J. D. A. AND SHAPIRO, A.: *J. Ment. Defic. Res.*, **6**: 38, 1962.
40. WANG, H. C. *et al.*: *Nature (London)*, **195**: 733, 1962.
41. FÖLLING A.: *Hoppe Seyler Z. Physiol. Chem.*, **227**: 169, 1934.
42. STANBURY, J. B. AND HEDGE, A. N.: *J. Clin. Endocr.*, **10**: 1471, 1950.
43. ALLAN, J. D. *et al.*: *Lancet*, **1**: 182, 1958.
44. STANBURY, J. B., OHELA, K. AND PITT-RIVERS, R.: *J. Clin. Endocr.*, **15**: 54, 1955.
45. MCGIRR, E. M., HUTCHISON, J. H. AND CLEMENT, W. E.: *Scot. Med. J.*, **4**: 107, 1959.
46. TOWNSEND, E. H., JR., MASON, H. H. AND STRONG, P. S.: *Pediatrics*, **7**: 760, 1951.
47. WESTALL, R. G., DANCIS, J. AND MILLER, S.: *A.M.A. J. Dis. Child.*, **94**: 571, 1957 (abstract).
48. RUSSELL. A. *et al.*: *Lancet*, **2**: 699, 1962.
49. MCMURRAY, W. C. *et al.*: *Ibid.*, **1**: 138, 1962.
50. HARRIS, H., PENROSE, L. S. AND THOMAS, D. H. H.: *Ann. Hum. Genet.*, **23**: 442, 1959.